A Single Nucleotide Polymorphism in the CYP4F2 but not CYP4A11 Gene Is Associated With Increased 20-HETE Excretion and Blood Pressure

Natalie C. Ward, I-Jung Tsai, Anne Barden, Frank M. van Bockxmeer, Ian B. Puddey, Jonathan M. Hodgson, Kevin D. Croft

Abstract—Arachidonic acid is a major fatty acid that can be metabolized by the cytochrome P450 enzyme to a number of bioactive eicosanoids. A major metabolite of this oxidation is 20-hydroxyeicosatetraenoic acid, which acts as a potent vasoconstrictor. However, in the kidney, its vasoconstrictor actions can be offset by its natriuretic properties. A guanine-to-adenine polymorphism in the CYP4F2 gene was associated with a reduction in 20-hydroxyeicosatetraenoic acid production in vitro. A thymidine-to-cytosine polymorphism in the CYP4A11 gene reduced catalytic activity by >50% in vitro and was associated with hypertension. The aim was to determine whether these 2 mutations are associated with urinary 20-hydroxyeicosatetraenoic acid excretion and blood pressure in humans. For the CYP4F2, 51% were homozygous for the G allele, 40% were carriers, and 9% were homozygous for the A allele. For CYP4A11, 72% were homozygous for the T allele, 25% were carriers, and 3% were homozygous for the C allele. The CYP4F2 GA/AA genotype was significantly associated with an increase in both 20-hydroxyeicosatetraenoic acid excretion and systolic blood pressure. The CYP4A11 CC/TC genotype was significantly associated with a reduction in 20-hydroxyeicosatetraenoic acid excretion but was not associated with blood pressure. We have demonstrated for the first time in humans that polymorphisms of the CYP4F2 and CYP4A11 genes have opposite effects on 20-hydroxyeicosatetraenoic acid excretion. The positive association between the CYP4F2 GA/AA genotype and both systolic blood pressure and 20-hydroxyeicosatetraenoic acid excretion strengthens a role for 20-hydroxyeicosatetraenoic acid in the modulation of blood pressure. (Hypertension. 2008;51:1393-1398.)

Key Words: cytochrome P450 ▪ CYP4F2 V433M ▪ CYP4A11 F434S ▪ 20-HETE ▪ blood pressure

Arachidonic acid is a major membrane fatty acid that can be metabolized by the cytochrome P450 (CYP450) enzymes to a range of bioactive compounds. These compounds are thought to play a central role in the regulation of blood pressure (BP), vascular tone, and renal function.1,2 Within the vasculature, the CYP450 enzymes belonging to the 2-gene family (CYP 2B, 2C8, 2C9, 2C10, and 2J2) are responsible for the production of epoxides, whereas the α-hydroxylases belonging to the CYP 4A and 4F families are involved in the production of hydroxyeicosatetraenoic acids (HETEs).3,4 Animal studies have previously shown that disruption of the murine Cyp450 4a14 gene results in hypertension, possibly via increased expression of Cyp4a12.5 20-HETE has been shown to play a role in vasoconstriction and renal salt handling in the spontaneously hypertensive rat.5,6,7 In humans, 20-HETE has been shown to play a role in regulation of natriuresis in salt-sensitive and salt-resistant hypertension,8 and we have previously demonstrated a significant association between urinary 20-HETE excretion and both hypertension and endothelial dysfunction.10 Paradoxically, within the kidney, 20-HETE can have either prohypertensive or antihypertensive actions, depending on its site of production. In the renal tubule, 20-HETE inhibits tubular sodium reabsorption, resulting in a natriuresis, and has antihypertensive properties,1,2 whereas in the renal vasculature, 20-HETE acts as a vasoconstrictor and is prohypertensive.2 The CYP4F2 and CYP4A11 enzymes function as renal 20-HETE synthases in humans,3,4,11 with the CYP4F2 isoform thought to account for ≈70% of the 20-HETE production in human renal microsomes.3 On the CYP4F2 gene, a guanine-to-adenine missense transition at nucleotide 1347 results in a nonsynonymous valine-to-methionine amino acid substitution at residue 433. A recent in vitro study has shown that transfection of this single nucleotide polymorphism into Sf9 insect cells using recombinant baculoviruses results in an ≈50% reduction in 20-HETE production.3 For the CYP4A11 gene, a thymidine-to-cytosine missense transition at nucleotide 8590 results in a nonsynonymous phenylalanine-to-
serine amino acid substitution at residue 434. This mutation has been shown to have little effect on the enzyme’s affinity for arachidonic acid but does reduce the enzymatic activity by >50% in vitro. Furthermore, this loss-of-function mutation has been associated with hypertension in a white, but not African American, population. The authors postulated that the elevation in BP may be because of effects of reduced 20-HETE production on renal sodium transport; however, urinary 20-HETE excretion was not measured.

To date, no studies have examined either mutation in a human population and their relationship with both urinary 20-HETE excretion and BP. Therefore, the aim of this study was to examine the relationships between the CYP4F2 V433M and CYP4A11 F434S polymorphisms and both 20-HETE excretion and BP in humans.

Methods
Study Protocol
DNA was extracted from peripheral blood leukocytes using a Triton X-100 and salt-out procedure modified from Miller et al. The cohort consisted of 235 (129 men and 106 women) predominately white individuals (97%) who had been recruited previously to the University of Western Australia School of Medicine and Pharmacology to investigate lifestyle effects on BP. The group consisted of normotensive individuals (n=74) and both treated and untreated hypertensive subjects (n=161: 86 treated and 75 untreated). None of the participants were taking any antioxidant and/or vitamin preparations for ≥3 weeks before study entry. Smokers and individuals with diabetes were excluded from the study. The studies were approved by the Royal Perth Hospital and University of Western Australia Human ethics committees. All of the participants provided a written informed consent before entry into the study.

24-Hour Ambulatory BP Monitoring
Twenty-four–hour ambulatory BP was measured with a Spacelabs 90207 monitor fitted by a trained researcher, as described previously. Briefly, an internal standard, [2H2]-20-HETE (2 ng) was added to all of the urine samples (2 mL) before incubation with glucuronidase to free all of the conjugated 20-HETE. After hydrolysis, samples were extracted using Bond Elut-Certify II cartridges before high-performance liquid chromatography purification, formation of the TBDMS-PFB derivative, and finally gas chromatography/mass spectrometry analysis in select ion monitoring mode using negative chemical ionization. Ions monitored were m/z 433 and m/z 435 for 20-HETE and the deuterium-labeled internal standard, respectively. The interassay coefficient of variation was 10%.

Biochemistry
Twenty-four–hour urinary sodium was analyzed using an ion-selective electrode unit and serum and urinary creatinine using a standard kinetic colorimetric assay. Renal function was calculated using a modified glomerular filtration rate, as outlined by Kidney Health Australia (www.kidney.org.au). The subject characteristics are described in Table 1. Of the 235 individuals, 161 were hypertensive, as defined by a

<table>
<thead>
<tr>
<th>Table 1. Subject Characteristics</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>N</td>
</tr>
<tr>
<td>Gender, male/female</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m²</td>
</tr>
<tr>
<td>CYP4F2 genotype, n (%)*</td>
</tr>
<tr>
<td>AA</td>
</tr>
<tr>
<td>GA</td>
</tr>
<tr>
<td>GG</td>
</tr>
<tr>
<td>CYP4A11 genotype, n (%)*</td>
</tr>
<tr>
<td>CC</td>
</tr>
<tr>
<td>TC</td>
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<tr>
<td>TT</td>
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</table>

Based on this, we had 90% power, with P=0.05 to detect this difference. Independent Student t tests and ANOVA were used to compare means. Linear regression analysis was used to determine whether either the CYP4F2 V433M or CYP4A11 F434S mutation predicted 20-HETE excretion and BP, after adjustment for variables including age, gender, and body mass index (BMI). Binary logistical regression analysis was carried out to determine the effect of either genotype on the prevalence of hypertension (odds ratios and 95% CIs). Bonferroni adjustment for multiple testing was included in all of the statistical analyses.

Statistical Analysis
Statistical analysis was performed using SPSS version 15.0 (SPSS Inc). To determine whether the CYP4F2 and CYP4A11 mutations were in Hardy-Weinberg equilibrium, observed and predicted genotype counts were compared using a χ² test. There was close agreement between observed and expected counts, with no departures from Hardy-Weinberg equilibrium. Power calculations were based on detecting a difference of 100 pmol/24 hours in urinary 20-HETE excretion between the recessive and nonrecessive groups. Based on this, we had 90% power, with P=0.05 to detect this difference. Independent Student t tests and ANOVA were used to compare means. Linear regression analysis was used to determine whether either the CYP4F2 V433M or CYP4A11 F434S mutation predicted 20-HETE excretion and BP, after adjustment for variables including age, gender, and body mass index (BMI). Binary logistical regression analysis was carried out to determine the effect of either genotype on the prevalence of hypertension (odds ratios and 95% CIs). Bonferroni adjustment for multiple testing was included in all of the statistical analyses.

Results
Subject Characteristics
The subject characteristics are described in Table 1. Of the 235 individuals, 161 were hypertensive, as defined by a

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT</th>
<th>HT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic BP, mm Hg</td>
<td>116/71</td>
<td>137/80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-h BP, mm Hg</td>
<td>115/69</td>
<td>136/82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>20-HETE, geometric mean (95% CI), pmol/24 h</td>
<td>545 (448 to 662)</td>
<td>690 (616 to 773)</td>
<td>0.039</td>
</tr>
<tr>
<td>Urinary sodium excretion, mean ± SD, mmol/24 h</td>
<td>154 ± 64</td>
<td>62 (38.5)</td>
<td>0.410</td>
</tr>
</tbody>
</table>

NT indicates normotensive; HT, hypertensive.
*Data are by χ² analysis.
24-hour ambulatory BP >125/80 mm Hg, a clinic BP >140/90 mm Hg, or current use of antihypertensive medication. The hypertensive individuals were significantly older and had a higher BMI than the normotensive individuals. Within the hypertensive individuals, 3% were of Asian ethnicity, whereas 4% of normotensive individuals were Asian. All of the other individuals were white. The hypertensive subjects had significantly higher urinary 20-HETE excretion when compared with the normotensive individuals. Within the whole group the CYP4F2 GG genotype (wild-type) was present in 51% of individuals, the GA genotype in 40%, and the AA genotype in 9%. The CYP4A11 TT genotype (wild-type) was present in 72% of individuals, the TC genotype in 25% and the CC genotype in 3%. There was no difference in the frequency of the genotypes between the 2 groups (Table 1).

**Urinary 20-HETE and Correlations With Clinical Variables**
Within the whole group, there were significant positive correlations between urinary 20-HETE excretion and 24-hour systolic BP (r=0.147; P=0.039), 24-hour diastolic BP (r=0.203; P=0.004), BMI (r=0.225; P=0.001), modified glomerular filtration rate (r=0.144; P=0.035), and 24-hour urinary sodium excretion (r=0.179; P=0.009). Only the correlation with BMI (r=0.024) remained significant after adjustment for gender.

**Genotype Analysis**
The initial analysis of the CYP4F2 genotypes revealed no significant differences when the AA genotype was considered relative to the GG/GA (a recessive effect model). In addition, the initial analysis of the CYP4A11 genotypes demonstrated no significant differences when the CC genotype was considered relative to TT/TC (a recessive effect model), although, in both cases, statistical power is limited by the small number of cases with these recessive genotypes, 21 (9%) and 7 (3%), respectively. Based on our initial analysis and the work by Gainer et al, the results were analyzed using a dominant-effect model for both the CYP4F2 (GG versus GA/AA) and CYP4A11 (TT versus TC/CC) enzymes.

**Effect of the CYP4F2 Polymorphism on 20-HETE and BP**
Analysis of the CYP4F2 genotype revealed that individuals with the GA/AA genotype had significantly increased 24-hour urinary 20-HETE excretion compared with those with the wild-type GG genotype (Figure 1A). Linear regression analysis revealed that having the CYP4F2 GA/AA genotype was associated with significantly increased urinary 20-HETE excretion, both before and after adjustment for age and BMI (Table 2). When gender was added to the model, the relationship between the CYP4F2 GA/AA genotype and 20-HETE was attenuated (Table 2). Analysis of a gene/gender interaction for effects on 20-HETE was not significant (P=0.577). Further adjustment for the presence of hypertension or the use of antihypertensive medication did not alter these results. Adjustment for multiple testing also attenuated the relationship.

BP analysis revealed that individuals having the CYP4F2 GA/AA genotype had significantly elevated systolic BP (Figure 2A), but not diastolic BP (Figure 2B), compared with those with the GG genotype, after adjustment for age and BMI. A further addition of gender to the linear regression model attenuated this result (Table 2). Analysis of a gene/gender interaction for effects on BP revealed no significant interaction for either systolic (P=0.428) or diastolic (P=0.232) BP. Separate analysis of the genders revealed significantly higher systolic BP in women carrying the GA/AA genotype compared with the GG genotype (129.1±1.9 versus 123.8±1.7 mm Hg; P=0.038) but not in men (134.8±1.8 versus 132.8±1.8 mm Hg; P=0.404). There was no association with an increased prevalence of hypertension in those with the CYP4F2 GA/AA genotype (odds ratio: 1.18; 95% CI: 0.66 to 2.09).

**Table 2. Linear Regression Analysis With the CYP4F2 GA/AA or CYP4A11 CC/TC Genotype as the Independent Variable**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CYP4F2 GA/AA</th>
<th>CYP4A11 CC/TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary 20-HETE, pmol/24 h</td>
<td>0.043</td>
<td>0.064</td>
</tr>
<tr>
<td>Urinary 20-HETE, pmol/24 h*</td>
<td>0.042</td>
<td>0.076</td>
</tr>
<tr>
<td>Urinary 20-HETE, pmol/24 h†</td>
<td>0.058</td>
<td>0.056</td>
</tr>
<tr>
<td>24-h systolic BP, mm Hg</td>
<td>1.86</td>
<td>2.08</td>
</tr>
<tr>
<td>24-h diastolic BP, mm Hg*</td>
<td>3.01</td>
<td>2.79</td>
</tr>
</tbody>
</table>

*Age and BMI are included in the model.
†Age, BMI, and gender are included in the model.
Effect of the CYP4A11 Polymorphism on 20-HETE and BP

In contrast to CYP4F2, analysis of the CYP4A11 genotype demonstrated that individuals with the TC/CC genotype had significantly lower urinary 20-HETE excretion compared with those with the TT genotype (Figure 1B), and this remained significant after adjustment for multiple testing. The CYP4A11 TC/CC genotype was a borderline significant predictor of reduced urinary 20-HETE excretion, both before and after adjustment for age and BMI (Table 2). When gender was added to the model, this did not affect the CYP4A11 CC/TC relationship (Table 2). Analysis of a gene-gender interaction for effects on 20-HETE was not significant ($P=0.669$). Further adjustment for the presence of hypertension or the use of antihypertensive medication did not alter these results.

There were no significant differences in either systolic or diastolic BP between the TC/CC and TT genotypes of the CYP4A11 gene (Figure 2C and 2D). There was no significant gene-gender interaction for effects on systolic ($P=0.868$) or diastolic ($P=0.823$) BP. Separation of the genders revealed no significant differences in BP for men or women for the CYP4A11 genotype (systolic BP: men, 134.7±2.3 versus 133.4±1.5 mm Hg, $P=0.632$; women, 127.1±2.5 versus 125.8±1.5 mm Hg, $P=0.678$). In linear regression analysis, having the CYP4A11 CC/TC genotype did not predict either systolic or diastolic BP. There was no association with an increased prevalence of hypertension in those with the CYP4A11 CC/TC genotype (odds ratio: 1.14; 95% CI: 0.60 to 2.20).

Effect of Having Both the CYP4F2 and CYP4A11 Polymorphisms on 20-HETE and BP

A further observation of these mutations within the whole group examined the relationship between having both polymorphisms and both urinary 20-HETE excretion and BP. Analysis of urinary 20-HETE excretion revealed the GA/AA-only group to have the highest levels; the TC/CC group had the lowest, whereas the group that had both polymorphisms was similar to the wild-type (Figure 3). After adjustment for multiple testing, only the difference between the GA/AA-only and TC/CC-only groups remained significant ($P=0.044$). In contrast, BP was not significantly affected by those with both polymorphisms (Table 3).

Discussion

The present study has shown for the first time in humans that the CYP4F2 V433M polymorphism is associated with increased urinary 20-HETE excretion and elevated systolic BP. Although it remains to be established whether urinary excretion of 20-HETE reflects renal production, these results suggest that this polymorphism may contribute, either directly or indirectly, to an increase in urinary 20-HETE excretion. The relationship seen between the CYP4F2 mutation and elevated BP may be because of the observed increase...
in 20-HETE, or it maybe that the increase in BP contributes to an increase in renal 20-HETE.

Immunoprecipitation studies suggest that the CYP4F2 isoform accounts for \( \leq 70\% \) of the 20-HETE production in renal microsomes.\(^{19}\) Our results are in contrast to the in vitro finding of Stec et al,\(^3\) who demonstrated that Sf9 insect cells transfected with the CYP4F2 mutation had reduced production of 20-HETE. Stec et al\(^3\) transfected cells with CYP4F2 recombinant baculoviruses cloned from human cDNA derived from RNA isolated from a number of different organs and measured their ability to produce 20-HETE. In our study, we measured 24-hour urinary 20-HETE excretion in both hypertensive and normotensive individuals and related the levels to the presence of the polymorphism. The reason for this discrepancy is unclear. Although it is possible that the CYP4F2 mutation is an activating mutation in humans, this is unlikely given the results of the in vitro transfection data.\(^3\)

Instead, it is probable that, in humans, there are a large number of factors influencing both the activity of the enzyme and the level of 20-HETE produced. These factors include endogenous levels of arachidonic acid substrate, re-esterification of 20-HETE into phospholipids, and the influence of sodium balance, sympathetic activity, and levels of endogenous mediators of 20-HETE synthesis, such as androgens, NO, angiotensin II, and endothelin-1. It is also possible that the CYP4F2 mutation does result in a decrease in 20-HETE production, as shown by Stec et al,\(^3\) but that this then leads to a homeostatic increase in renal 20-HETE production, possibly via upregulation of other CYP450 isoforms. Furthermore, it remains unclear exactly what measurement of urinary 20-HETE excretion represents: renal production, vascular production, increased metabolism, or a combination of these factors. Therefore, we cannot say with certainty that urinary 20-HETE excretion, as measured in this study, is directly related to either the CYP4F2 or CYP4A11 mutations. The difference in the effect of the CYP4F2 mutation on production of 20-HETE in the 2 studies highlights the complexity of examining the effects of genetic polymorphisms in human population studies compared with isolated cell systems. A limitation of the present study is that we have not determined the effect of either single nucleotide polymorphism on arachidonic acid metabolism in vitro, and further investigation of this is needed.

We have also shown that the CYP4A11 F434S polymorphism was associated with reduced urinary 20-HETE excretion but had no significant association with BP. Both the CYP4A11 F434S and CYP4F2 V433M genotype frequencies observed in the present study were in agreement with previous studies examining these mutations.\(^{3,11,20}\) Gainer et al\(^{11}\) had demonstrated previously an in vitro loss of function as a result of the CYP4A11 TC/CC genotype. The lack of an effect of the TC/CC genotype on BP in this cohort is intriguing. A previous study has shown a modest association between the TC/CC genotype and hypertension in white subjects.\(^{11}\) Although Mayer et al\(^{20}\) observed a tendency toward elevated BP in the CC genotype compared with TT/TC genotypes (recessive effect model), when the CC/TC genotypes were combined (dominant effect model), the association with high BP was lost.\(^{20,21}\) Both of these studies suggest that the CYP4A11 isoform is found at a location in the kidney where 20-HETE functions as a natriuretic, such that loss of production causes elevations in BP. The lack of a relationship between BP and individuals with the TC or CC genotype in our study could be because of the relatively small number of individuals with these genotypes. The use of antihypertensive agents did not account for the lack of an effect of the C allele on BP in our study, but we are unable to rule out the effects of sodium status, which was not assessed. Another possible explanation is that this enzyme is not a major isoform responsible for the production of 20-HETE or that the resulting fall in CYP4A11 activity may be counteracted by other homeostatic mechanisms, such as an increase in epoxygenase activity.

Gender has been shown to have a significant effect on BP and 20-HETE excretion. In the present study, men had significantly higher levels of 20-HETE excretion when compared with women (data not shown), and there were more men in the hypertensive group compared with women. Adjusting for gender in the regression models resulted in an attenuation of the relationship between the CYP4F2 GA/AA genotype and urinary 20-HETE excretion and systolic BP. Androgens have been shown to promote BP elevation, and there is evidence to suggest that this is because of increased production of 20-HETE.\(^{22}\) CYP450 enzymes are thought to be regulated by androgens, and a recent animal study has shown that inhibition of CYP4A activity prevents androgen-induced hypertension.\(^{23}\) Although we observed no gene-gender interaction for effects on 20-HETE excretion or BP, we may be limited by small numbers and cannot completely exclude gender effects on both hypertension and 20-HETE production.

We have also shown that the effects of having both the CYP4F2 and CYP4A11 polymorphisms on 20-HETE excretion differ from that of having either mutation alone. Although this did not translate to differences in BP, it does suggest that the CYP4A11 genotype has the ability to reduce 20-HETE excretion, and this may "protect" against the increase in 20-HETE excretion seen with the CYP4F2 GA/AA genotype. Alternatively, the CYP4F2 isoform may regulate the activity of the CYP4A11 isoform, and, thus, when both mutations are present, this mechanism is disrupted. However, the location and activity of all of the CYP450 isoforms in the human kidney are not complete, and

<table>
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<th>Variable</th>
<th>CYP4F2 GA/AA</th>
<th>CYP4A11 TC/CC</th>
<th>Both SNPs</th>
<th>Wild-Type</th>
<th>P</th>
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<tbody>
<tr>
<td>Systolic BP, mean±SD, mm Hg</td>
<td>131.3±1.6</td>
<td>128.5±2.4</td>
<td>134.2±2.6</td>
<td>128.2±1.5</td>
<td>0.164</td>
</tr>
<tr>
<td>Diastolic BP, mean±SD, mm Hg</td>
<td>79.0±1.1</td>
<td>77.2±1.7</td>
<td>79.2±1.8</td>
<td>78.0±1.1</td>
<td>0.752</td>
</tr>
</tbody>
</table>

SNP indicates single nucleotide polymorphism.
there are likely several isoforms of both CYP4A and CYP4F differentially expressed at different sites. In conclusion, the present study has demonstrated in humans, for the first time, a significant association with elevated systolic BP in individuals with the CYP4A11 TC/CC genotype. Furthermore, this genotype was associated with significantly increased urinary 20-HETE excretion. In addition, we observed significant decreases in 20-HETE excretion in individuals with the CYP4A11 TC/CC genotype. Although this was not related to any changes in BP, it confirms that this isoform is likely to influence 20-HETE within the kidney.

**Perspectives**

20-HETE is a major product of arachidonic acid metabolism by the cytochrome P450 4A and 4F enzymes. The major sites of 20-HETE production are in the vasculature and kidney, where it generally functions as a vasoconstrictor. However, it also has natriuretic properties when produced in the renal tubule, resulting in an antihypertensive effect. Several animal and human studies have demonstrated a role for 20-HETE in the pathogenesis of hypertension, although the exact mechanisms involved in its production, action, and regulation remain to be elucidated. This is particularly important when investigating the kidney, where 20-HETE can have both prohypertensive and antihypertensive actions. Indeed, the present study has highlighted the relationship between a single nucleotide polymorphism in 2 different CYP450 isoforms within the kidney and urinary 20-HETE excretion and BP. This could have important implications if considering the inhibition of 20-HETE production, because inhibitors will need to target specific sites of production and possibly specific isoforms of CYP450.

**Acknowledgment**

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**Disclosures**

None.

**References**

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